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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/562,290	06/20/2006	Helen Braven	ATLAS 9452 US	5797

39843 7590 01/31/2008  
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EXAMINER
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MARTIN, PAUL C

ART UNIT	PAPER NUMBER
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1657

MAIL DATE	DELIVERY MODE
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01/31/2008

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	Application No.	Applicant(s)	
	10/562,290	BRAVEN ET AL.	
	Examiner	Art Unit	
	Paul C. Martin	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 14 September 2007.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 19-36 is/are pending in the application.
- 4a) Of the above claim(s) 32-36 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 19-31 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 22 December 2005 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)            | 4) <input type="checkbox"/> Interview Summary (PTO-413)                 |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. _____  |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application       |
| Paper No(s)/Mail Date <u>10/24/06</u> .  | 6) <input checked="" type="checkbox"/> Other: <u>Notice to Comply</u> . |

## DETAILED ACTION

Claims 19-36 are pending in this application.

### *Election/Restrictions*

Applicant's election without traverse of Group I (Claims 19-31) in the reply filed on 09/14/07 is acknowledged. Claims 32-36 withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to non-elected inventions, there being no allowable generic or linking claim. Election was made **without** traverse.

Claims 19-31 were examined on their merits.

### *Specification*

This application contains sequence disclosures at pages 11, 12 and 19 that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with one or more of the requirements of 37 C.F.R. § 1.821 through 1.825 for one or more of the reasons set forth on the attached form "Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequences And/Or Amino Acid Sequence Disclosures".

Wherein attention is directed to paragraph(s) §1.82 (c) and (e). Although an examination of this application on the merits can proceed without prior compliance, compliance with the Sequence Rules is required for the response to this Office action to be complete.

The use of the trademarks Enzchek™, Trizma™, Biodyne™, Sephadex™ and Autolab™ has been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 19-31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 19 is drawn to a method of detecting protease activity by contacting a sample with a labeled protease substrate. However, it is unclear how every protease will be detected using any protease substrate.

For example, proteases are known to cleave certain substrates preferentially and one labeled substrate will not necessarily be recognized and cleaved by every protease. Claim 20-31 are rejected as being dependent upon rejected Claim 19.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 19 and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Hugli (US 6,235,494 B1).

Hugli teaches a method for detecting mannan-binding protein-associated serine protease (MASP) by contacting a sample of blood or plasma with a MASP protease electrochemically labeled (linked to) substrate and wherein cleavage of the site recognized by a MASP enzyme results in the electrochemical labels becoming detectable and thereby detecting the MASP enzyme in the sample (Column 53, Claims 1 and 6) and wherein the protease inhibitor Futhan is contacted with the sample solution (Column 41, Lines 30-36).

Claims 19, 20, 22 and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Ludin *et al.* (US 6,495,336 B1).

Ludin *et al.* teaches a method for detecting protease activity in a sample by contacting a sample solution with a protease substrate labeled (linked to) with an electrochemically active marker under conditions in which protease may cleave off the electrochemically active marker and detecting the electrochemically active marker using the amperometric technique of cyclic voltammetry (Columns 12, 13, 15 and 16, Claims 1, 11, 13).

Claims 19, 20, 22, 26, 28, 29 and 30 are rejected under 35 U.S.C. 102(b) as being anticipated by Nagy *et al.* (2000).

Nagy *et al.* teaches a method for detecting proline iminopeptidase (IP) activity in a sample solution by contacting the sample solution with the electrochemically labeled (linked to) IP substrates L-proline *p*-nitroanilide or L-proline  $\beta$ -naphthylamide under conditions suitable for IP to cleave the substrates and detecting the released *p*-nitroanilide or  $\beta$ -naphthylamide by the amperometric technique of cyclic voltammetry (Pg. 267, Schemes 1 and 2 and Pg. 268, Fig. 2) and wherein the level of IP activity is compared to a level of IP activity that is diagnostic of Bacterial (pathogen) Vaginosis (BV) a sexually transmitted disease, thereby detecting BV (Pg. 271, Column 1, Lines 1-15).

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 19, 20, 21, 22, 26, 28 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nagy *et al.* (2000) in view of Forrest *et al.* (US 4,978,610).

The teachings of Nagy *et al.* were discussed above.

Nagy *et al.* does not teach the use of differential pulse voltammetry to determine information about the electrochemically active marker.

Forrest *et al.* teaches that components which comprise an electroactively labeled reagent can be used in assays which measure a perturbation in the electrochemical characteristic of the components, and that this perturbation can be measured by differential pulse voltammetry, cyclic voltammetry or square wave voltammetry (Column 1, Lines 23-42).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the method of Nagy *et al.* for detecting proline iminopeptidase (IP) activity in a sample solution by cyclic voltammetry by using differential pulse voltammetry as taught by

Forrest *et al.* because they are art-recognized functionally equivalent techniques for measuring electrochemical activity. The use of alternatives and functional equivalent techniques would have been desirable to those of ordinary skill in the art based upon the economics and availability of detection apparatus as well as artisinal preference. There would have been a reasonable expectation of success in making this substitution because Nagy *et al.* teaches the use of cyclic voltammetry to measure electrochemical characteristics and Forrest *et al.* teaches that differential pulse voltammetry and cyclic voltammetry can be use to measure electrochemical characteristics.

Claims 19, 20, 22, 23, 26, 28 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nagy *et al.* (2000) in view of Nicholson (US 4,456,337).

The teachings of Nagy *et al.* were discussed above.

Nagy *et al.* does not teach the use of one or more electrodes that are functionally surrounded by a selectively permeable membrane.

Nicholson teaches a technique wherein two or more electrodes are functionally surrounded by a selectively permeable membrane which prevents loss of electrochemically generated reactant species as well as preventing contamination of the counter electrodes where these species could interfere with the counter electrodes (Column 6, Lines 6-35).



It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the method of Nagy *et al.* for detecting proline iminopeptidase (IP) activity in a sample solution by cyclic voltammetry by using a technique wherein two or more electrodes are functionally surrounded by a selectively permeable membrane as taught by Nicholson because the selectively permeable membrane would serve to prevent contamination of the electrodes from interferants both exogenous and endogenous to the assay. One of ordinary skill in the art would have been motivated to make this modification because of the advantages discussed by Nicholson such as preventing loss of electrochemically generated reactant species into the mixture milieu as well as serving to minimize contaminants interacting with the electrodes entering from the milieu. There would have been a reasonable expectation of success in making this modification because both techniques are drawn to the detection of electrochemically active components using multiple electrodes.

Claims 19, 24, 25, 26, 27 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hugli (US 6,235,494 B1) in view of Braven *et al.* (US 2005/0221315 A1).

The teachings of Hugli were discussed above.

Hugli does not teach wherein the electrochemically active marker is a metallocene or ferrocene moiety, wherein each protease substrate is labeled with more than one

electrochemically active marker or a method further comprising a step of contacting the sample solution with a putative protease inhibitor.

Braven *et al.* teaches a compound wherein an amino acid, peptide or protein is labeled with electrochemically active ferrocene and wherein the compound is, or becomes electrochemically active following cleavage (Pgs. 19 and 20, Claims 75, 78, 85 and 89) and wherein each compound can be labeled with up to four metallocene groups (Pg. 6, Paragraph [0042]).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the method for detecting mannan-binding protein-associated serine protease (MASP) by contacting a sample of blood or plasma with a MASP protease electrochemically labeled (linked to) substrate as taught by Hugli with the use of multiple electrochemically active ferrocene moieties as taught by Braven *et al.* because one of ordinary skill would have recognized that the ferrocene markers were as suitable for the purpose of electrochemical labeling of protein as the electrochemically active labeled protease substrates taught by Hugli. The MPEP states:

The selection of a known material based on its suitability for its intended use supported a

prima facie obviousness determination in *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 USPQ 297 (1945)

It would have been further obvious to one of ordinary skill in the art to label the substrate with multiple electrochemically active markers because this would provide a larger and more detectable signal than a single label. The MPEP also states:

*In re Harza*, 274 F.2d 669, 124 USPQ 378 (CCPA 1960) (Claims at issue were directed to a water-tight masonry structure wherein a water seal of flexible material fills the joints which form between adjacent pours of concrete. The claimed water seal has a “web” which lies in the joint, and a plurality of “ribs” projecting outwardly from each side of the web into one of the adjacent concrete slabs. The prior art disclosed a flexible water stop for preventing passage of water between masses of concrete in the shape of a plus sign (+). Although the reference did not disclose a plurality of ribs, the court held that mere duplication of parts has no patentable significance unless a new and unexpected result is produced.).

Claims 19, 20, 22, 23, 24, 26 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ludin *et al.* (US 6,495,336 B1) in view of Braven *et al.* (US 2005/0221315 A1).

The teachings of Ludin *et al.* were discussed above.

Ludin *et al.* does not teach wherein the electrochemically active marker is a metallocene or ferrocene moiety, wherein each protease substrate is labeled with more than one electrochemically active marker.

The teachings of Braven *et al.* were discussed above.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the method for detecting protease activity in a sample by contacting a sample solution with a protease substrate labeled (linked to) with an electrochemically active marker as taught by Ludin *et al.* with the use of multiple electrochemically active ferrocene moieties as taught by Braven *et al.* because one of ordinary skill would have recognized that the ferrocene markers were as suitable for the purpose of electrochemical labeling of protein as the electrochemically active aniline or aminoquinoline labeled protease substrates taught by Ludin *et al.* above.

The MPEP states:

The selection of a known material based on its suitability for its intended use supported a prima facie obviousness determination in *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 USPQ 297 (1945)

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at

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the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Paul C. Martin whose telephone number is 571-272-3348. The examiner can normally be reached on M-F 8am-4:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Paul Martin  
Examiner  
Art Unit 1657

01/25/08

/Jon P. Weber/  
Jon P. Weber  
Supervisory Patent Examiner, 1657

<b>Notice to Comply</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	10/562,290	BRAVEN ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	Paul C. Martin	1657	

**NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES**

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

- ☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).
- ☒ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).
- ☒ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).
- ☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."
- ☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).
- ☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable form of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).
- ☐ 7. Other:

**Applicant Must Provide:**

- ☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".
- ☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.
- ☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (571) 272-2510 or (571) 272-2533

For CRF Submission Help, call (571) 272-2510 or (571) 272-2533

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